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Chapter

Circulation of Cerebrospinal Fluid (CSF)

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Abstract

Circulation of cerebrospinal fluid (CSF) is a clear, colorless liquid that circulates between the ventricular system and the subarachnoid space. In addition to its function as a natural cushion for the brain, CSF provides the circulation of metabolic products, hormones, and neurotransmitters. Moreover, it has tasks such as maintaining the homeostatic balance of the central nervous system, protecting the brain against mechanical injuries, preventing direct contact of the brain with the extracellular region. It also has a role in maintaining cerebral interstitial fluid (ISF) homeostasis and neuronal regulation. Normal CSF production, its circulation, and absorption have a critical role for the development and functioning of the brain. In an average adult person, roughly 150 ml of CSF circulates at any given moment. The ventricular part accounts for about 17% of the total volume of fluid, with the rest located in the subarachnoid cisterns and space. CSF is produced at a rate of about 0.3–0.4 mL/min, translating to 18–25 mL/H and 430–530 mL/day.

Keywords: circulation of cerebrospinal fluid (CSF), production of CSF, absorption of CSF, cerebral interstitial fluid (ISF), physiology of circulation of CSF

1. Introduction

A large amount of cerebrospinal fluid (CSF) is produced in the choroid plexus in the lateral ventricle. This produced CSF reaches the 3rd ventricle via the foramen Monroe, from here to the 4th ventricle via the Aquaduct Sylvius, and passes to the subarachnoid space via the foramen Magendie and the foramen Luschkas. From here, the CSF moves upwards, reaching the interpedincular cistern through the prepontin cistern, and from here to the convexity through the chiasmatic cistern. The CSF circulating from the dorsal, however, reaches convexity via the quadrigeminal cistern, ambient cistern, and vena cerebri magna cistern through the cerebellar hemispheres. CSF also passes into the central canal through the spinal cord and into the spinal subarachnoid space [1]. Absorption occurs from the arachnoid villi to the venous sinuses [2, 3].

The choroid plexus consists of villi. Each villi is covered with monolayer cubic epithelium with cilia. These cells are located on a basal membrane consisting of collagen, fibroblast, and nerve fibers. In the middle of each villi is a capillary vessel with no tight connections between endothelial cells with a loose wall structure. The blood–brain barrier in the choroid plexus is not formed by the tight connections between endothelial cells in the capillaries, unlike the parenchyma, but by the tight connections between cells on the villi [4].

Tight junction on the apical surface of the epithelium above the basal membrane form the blood–brain barrier [2, 4]. The choroid plexus, the epandymal layer, and the parenchyma are the production sites of CSF. As a result of studying isolated choroid plexus preparations, it has been shown that the choroid plexus is responsible for the production of approximately 80% of the CSF. However, the extrachoroidal source of CSF is not well known [5]. The first step of choroidal secretion involves passive filtration of plasma from the choroidal capillaries along a pressure gradient to the choroidal interstitial compartment.

CSF production from the choroid plexus occurs as a two-step process [6]. The first stage in CSF production is the accumulation of ultrafiltrate in the villi, which leaks out of the vein as a result of hydrostatic pressure due to tight connections between endothelial cells from the capillaries in the middle of the villi. This accumulation is secreted by the choroid plexus cell by converting it into CSF. Ultrafiltrate, which accumulates on the side of the basal membrane, is transferred by the sodium-potassium pump which actively pumps sodium into the cell, while water passively enters the cell along with sodium. The same pump also helps chloride. In addition, chloride enters the cell independently of this pump. Fluid with CSF properties inside the cell is again actively released into the ventricular cavity by the cell wall facing the ventricle with the help of a sodium-potassium pump [4, 5]. In normal physiological conditions, CSF production is not affected by intracranial pressure, but when intracranial pressure increases, there may be a decrease in CSF production, as it will affect ultrafiltrate production, which is the first stage of CSF production [5]. Changes in body temperature and serum osmolarity are not effective in CSF production [6].

CSF absorption occurs in arachnoid granulations located along the superior sagittal sinus. Coming from the subarachnoid region to the venous lakes in the arachnoid granulations, the CSF is absorbed into the cerebral veins. It is believed that these pathways work more, especially during an increase in intracranial pressure. CSF absorption is sensitive to pressure. CSF absorption increases when intracranial pressure increases, and absorption decreases if it is below the basal value [4, 7]. This is followed by the bulk ion transport from blood to CSF which occurs via the transcellular pathway facilitated by membrane ion carrier proteins and cytoplasmic carbonic anhydrase. Carbonic anhydrases catalyze the conversion of H_2O and CO_2 to H^+ and HCO_3. Transcellular transport of sodium (Na^+) and chloride (Cl^-) (together with HCO_3) are the most important ions carried by the choroid plexus epithelium, forming the osmotic gradient that activates H_2O secretion [8].

ATP-dependent ion pumps of the apical membrane allow the passage of Na^+, Cl^-, HCO_3, and Potassium (K^+) ions towards the ventricular lumen, forming the electrochemical gradient for CSF secretion. Transepithelial water movement also occurs through the transcellular pathway. It follows the osmotic gradient created by ATP dependent mechanisms and is facilitated by the aquaporins (AQP1) of the apical basolateral and luminal membranes [8, 9].

Aquaporins, which have different variations in the body, are found in many tissues. It has tissue specific variants. They are expressed in various secretory epithelium. For example, AQP1 and AQP5 are expressed in the pancreas, AQP3 and AQP5 are expressed in the salivary glands. AQP1 is abundantly expressed in the choroid plexus epithelium and contributes to the high water permeability of the membrane [8].

There are some substances that affect CSF production, and one of these substances is furosemide. Feurosemide's mechanism has little effect on carbonic anhydrase, but its main effect is that it can reduce CSF production by stopping chloride entering the cell. Another substance is acetazolamide, which causes a decrease in CSF production in humans and experimental models by blocking the carbonic anhydrase enzyme in the cell [5].

In physiological conditions, the rate of CSF production should be equal to the rate of absorption. Given that production and absorption occur in different parts of the system, it is assumed that its flow rate will be affected [9].

Oreskovic and Klarica studied the effects of the choroid in CSF physiology via plexectomies [9]. According to classical theory, a large decrease in the overall secretion of CSF is expected when choroid plexectomy is performed, and therefore some pressure relief can be achieved in patients with hydrocephalus with this method. Studies have shown that two-thirds of patients treated for a recurrence of hydrocephalus should be shunted [10].

The choroid plexectomy study conducted by Oreskovic and Klarica on rhesus monkeys showed that the chemical component of CSF remained normal, suggesting that the choroid plexus played a less role in molecular transport [11]. While there is evidence to support these claims regarding CSF production, there is also a large amount of literature describing the tides and the net flow of CSF [12].

According to Spector, active secretion and absorption of CSF are carried out by movable cilia located in the ependymal wall. CSF involves the transport of growth factors to certain areas of the brain in the circulatory system [12]. The composition of cerebrospinal fluid, CSF, consists mainly of 99% of water, while the remaining 1% consists of proteins, ions, neurotransmitters, and glucose [8, 13, 14]. The concentration, total viscosity, and surface tension of each of these proteins found in CSF vary in different conditions [15, 16], CSF absorption increases, and if below the basal value, absorption decreases [4, 17].

This is followed by the bulk ion transport from blood to CSF which occurs via the transcellular pathway facilitated by membrane ion carrier proteins and cytoplasmic carbonic anhydrase. Carbonic anhydrases catalyze the conversion of H_2O and CO_2 to H^+ and HCO_3. Transcellular transport of Na^+ and Cl^- (together with HCO_3) are the most important ions carried by the choroid plexus epithelium, forming the osmotic gradient that activates H_2O secretion [8].

The composition of CSF differs from serum due to different expressions of membrane-associated channels and transport proteins, which in this case causes the choroidal epithelium to be unidirectional [18]. On the apical side, epithelial cells are interconnected by tight junction that limit the movement of these molecules, and intercellular space connections form the blood–brain barrier. The apical side of the epithelium is covered with microvilli, while the basolateral side has folds that increase the surface area of the cells and make it more suitable for absorption.

Compared to plasma, CSF usually contain high concentrations of sodium (Na^+), chloride (Cl^-), and magnesium (Mg^{+2}), while lower concentrations contain potassium (K^-) and calcium (Ca^{+2}) [14]. On the apical side, active transport pumps release ions into the ventricular cavities. The movement of water in the apical membrane has been shown to be caused by the presence of aquaporin 1 (AQP1). Indeed, a study by Mobasheri and Marples revealed that the choroid plexus is among the tissues with the highest expression of AQP1 in the body [19].

Many studies have different conclusions regarding the AQP 4 as the main candidate for water transport in the basolateral membrane. The common focus of the studies has been the study of disease conditions that affect the production, absorption, or composition of CSF. Apart from its mechanical role, CSF has an important role in biochemical homeostasis throughout the CNS [12].

By using new techniques to analyze the diversity of CSF components, proteins, lipids, hormones and microRNAs, it will be possible to track the development of the disease over time in disease conditions [20]. The production and absorption of some CSF biomolecules, such as growth factors, neurotransmitters, cytokines, extracellular matrix proteins, permeability-related proteins, binding proteins, and

adhesion molecules can affect CSF homeostasis. Similarly, the microenvironment surrounding periventricular cells and their activities may vary in disease states [20].

CSF production is regulated by the autonomic nervous system and neuropeptides such as dopamine and atrial natriuretic peptide. The sympathetic nervous system reduces CSF production, while the cholinergic system increases its production. There is a circadian rhythm in CSF production [21]. Most of the hormones that regulate systemic water and electrolyte homeostasis, such as aldosterone, angiotensin II, and arginine vasopressin, are also present in the choroid plexus and ventricular system. These hormones are believed to have two tasks: the first is the production of CSF locally, and the second is the regulation of extracellular fluid in the brain, but they also have tasks in the central regulation of blood pressure [8]. CSF production can be reduced by the administration of diuretics and carbonic anhydrase inhibitors. In addition, any increase in intraventricular pressure can reduce plasma filtration and, as a result, CSF production by lowering the pressure gradient in the blood–brain barrier. In CSF and interstitial brain fluid, water and solutes change constantly, and this balance provides an optimal environment for neurons. This is directly proportional to the rate of formation of CSF and inversely proportional to the volume of CSF. In aging, there is less efficient active transport, with a slower CSF cycle causing the accumulation of potentially harmful metabolites in the interstitium of the brain. Clearance of brain metabolites per minute depends on the CSF regeneration at a rate of 0.3–0.4%. Brain catabolites form when fluid turnover rates drop by more than 50%, and the reduction in amyloid b decrease in CSF clearance is now believed to be associated with the development of Alzheimer's disease [22].

After production, CSF movement is usually carried out through the ventricular system, while it is also supported by the cilia ependyma [23]. The net flow of the CSF passes through the ventricular system, starting from the lateral ventricles [24]. The CSF flows from the lateral ventricles, through the left and right foramen of the Monro to the third ventricle. Then, it passes to the 4th ventricles. From the fourth ventricle, the CSF may flow laterally from the foramen of Lushka, or medially from the foramen of Magendie to the subarachnoid space. Passing through the foramen of Magendie results in the filling of the spinal subarachnoid space. CSF outflow from the foramen of Luschka goes into the subarachnoid space of cisterns and into the subarachnoid space that covers the cerebral cortex. CSF from the subarachnoid space is eventually reabsorbed into the superior sagittal sinus (SSS), known as the arachnoid. Arachnoid granulations provide reabsorption of CSF into the bloodstream by a pressure-dependent gradient [6]. In arachnoid granulations, outlets towards the CNS are seen due to the fact that the pressure in the subarachnoid space is greater than the venous sinus pressure. Similar to new theories about CSF production, there are also absorption theories. Studies in animal models have revealed that CSF can also be significantly absorbed through cervical lymphatics [6].

CSF, which is not reabsorbed by arachnoid granulations, can reach cervical lymphatics in two alternative ways. The first is along the subarachnoid space of the emerging cranial nerves [6]. This provides a direct route through which CSF can be transferred from cisterns to extracranial lymphatics. The second way in which CSF can reach lymphatics is through the Virchow-Robin space of the arteries and veins that penetrate the parenchyma of the brain [25].

The Virchow-Robin Space (VRS) is the area surrounding the arteries and veins of the brain parenchyma, which can vary in size depending on disease status. When the CSF is not absorbed by the classical way, it can enter the VRS or be directed to the brain interstitial fluid (ISF). The brain interstitial fluid ISF is believed to be a compartment with a subarachnoid space (SAS) that is mediated by AQP s and bidirectional flow to VRS, but it is not yet clear. If the CSF enters the ISF, it will

either be reabsorbed into the bloodstream, or it will enter the VRS, or it will enter the subarachnoid space again. From the VRS, CSF can reenter into the SAS or be reabsorbed by cervical lymphatics, depending on the forces exerted by cardiac pulsations and pulmonary respiration. In addition to the circulation of CSF to cervical lymphatics, studies have also been conducted explaining the reabsorption of CSF to the dural venous plexus. Arachnoid granulations at birth are not fully developed, and CSF absorption is based on the venous plexus of the inner surface of dura, which is more robust in infants [26]. Although not common in adults, the dural venous plexus is believed to play a role in absorption. Adult and fetal cadaver dissections and animal models with intradural injection have all been shown to fill the parasagittal dural venous plexus [27].

2. Physiology of circulation of cerebrospinal fluid

The CSF physiology, in the classical sense, is based mainly on animal experiments [28]. In recent research, the structure of CSF circulation has been questioned, challenging significant aspects of the classical model. Recently, CSF production and absorption have been reevaluated [9, 29–31].

According to the classical view described by Cushing in 1926 as the "third circulation" [32, 33], CSF flows from the ventricular system through the Lushka and Magendie foramen into the subaracanoid area in a one-way, rostrocaudal manner. The CSF then continues to flow either downwards around the spinal cord or upwards over the cerebral convexities, and is eventually absorbed by arachnoid granulations and arachnoidal villi on either side of the upper sagittal sinus.

Recent studies have highlighted a secondary pathway of CSF, circulation through perivascular VRS, similar to the lymphatic system in other parts of the body [34, 35]. This CSF circulatory system, which has a similar function to the lymphatic system with the participation of astroglia, has been called the "glymphatic system" [36, 37]. The glial membrane of the brain consists of the astrocytic end-feet and forms theVRS, it has high amounts of aquaporin channels and facilitates CSF transfer from VRS to the interstitial space of the brain cavity is cleaned and then empty the drainage paths paravenous makes it easy to carry along [36]. The in vivo imaging taken using fluorescent substances in mice also showed how this microcirculation removes amyloid beta and other waste products from the central nervous system [34].

CSF flow is pulsatile and depends on pulsational arterial perfusion. A central ventricular pulse wave is formed, followed by brain expansion, followed by a subarachnoid CSF frontooccipital pulse wave [38]. During systole, blood flows into the brain, expanding into the brain, compressing the ventricles and the cortical vessels outwards and SAS. Inward expansion of the brain leads to the pulsatile transfer of CSF from the the cerebral aqueduct and the rest of the ventricular system. During diastole, the volume of the brain decreases, and CSF flows in the opposite direction along the the cerebral aqueduct and the foramen magnum. The movement of CSF to the brain through VRS is also supported by arterial vibrations [35]. This suggests a link between decreased arterial pulses, which are often seen in some elderly patients, and amyloid B accumulation in Alzheimer's disease [36, 37]. Although in-vivo studies in humans are needed to confirm these findings, there is growing evidence that plaque may be another key site for extracranial output [24, 39].

Since Cushing, the collective flow character of CSF circulation has been accepted by most researchers. Even in recent studies, it is assumed that the CSF circulation is directed towards the arachnoid villus along the ventricles and subarachnoid space [24, 40]. VRS are a histologically defined anatomical area surrounding blood vessels

as they enter the brain tissue from the subarachnoid space Initially, VRSs were believed to be connected to the subarachnoid space, allowing for free fluid transfer. This concept was later elucidated by microscopic investigations that showed perivascular cavities as dead ends, open to the subarachnoid space but closed to the parenchyma, and therefore not a channel for flow [41].

Considering the microscopic anatomy of VRS, its thin structure is actually located on layers of endothelial, pial, and glial cells, each defined by different basal membranes [42]. The glia covering the brain parenchyma forms the outer wall of the VRSs [43]. In the capillary bed, the basal membrane of the glia merges with the outer vascular membrane, forming the VRS [44].

The arterial and venous vessels, which are located in the cortical subarachnoid space (SAS), are covered by a layer of pial cells that surround the vessels. The pial sheath forms a cavity next to the vessel wall, called the perivascular space (PVS) [45]. At the entrance of the cortical vessels to the VRS, the pial sheaths merge with the layer of pial cells lining the brain surface, forming a funnel-like structure that accompanies the VRS to the vessels only for a short distance [46]. However, the pial sheath of the arterial vessels extends to the VRS. Near the capillary bed, the pial sheath becomes more and more windowed and leaky [45].

Some authors use the terms "Virchow-Robin space" and "perivascular space" as synonyms [47], while others use the terms to name different areas as discussed above [48]. Studies with electron microscopy show that pial membranes separate VRS from the cortical subarachnoid space [46]. Since electron microscopy of human brain samples shows that VRS and PVS have collapsed, it has been a matter of debate whether these histologically characterized compartments are really openings or spaces [45]. However, studies in rodents have shown that VRS is filled with fluid, electron microscopic dense material [46], macrophages and other inflammatory cells [42].

Although pial cell layers separate the VRS from the cortical subarachnoid space, physiologically there is strong evidence that fluid circulates throughout the VRS. There are species-related differences in the pial layer. In mice, for example, the pial layer is very thin, while in humans it is thicker [49].

In humans, the pial sheath is described as a sensitive but seemingly continuous layer of cells, connected by desmosomes and cavity connections but without obvious tight connections [50]. As a result of numerous experimental studies, it has been recognized that the pia mater does not have permeable properties against liquids [51]. Given that the flow within the VRS depends on the pulsatility of the arteries [52], hydrostatic forces can move liquids and solutes along the pial membranes. However, while VRS basically allows for a two-way exchange between CSF and ISF, there is not much data to explain the scope and kinetics of such fluid movements.

Although it has been shown that the pial membranes between PVS and SAS can prevent the exchange of larger molecules, the intraparenchymal injection has not been shown to spread to cisternal CSF, although it has accumulated in PVS [53]. This observation is supported by clinical findings that red blood cells are confined in the subarachnoid space and do not enter the VRS following aneurysm rupture in humans [49]. It has been shown both experimentally and clinically that PVS, and possibly, more importantly, pathways between the essential membranes of arterioles and the wall of arteries, provide drainage for ISF and the brain's waste molecules.

There is experimental evidence that paraarterial drainage pathways are connected to the lymphatics of the posterior skull base [54]. In reality, the solutes and fluids can be discharged through the VRS from the brain interstitium through the arteries, into the cervical lymphatics [55]. This view was supported experimentally by immunohistochemical and confocal microscopic observations showing that

fluorescent dyes such as 3 kD dextran or 40 kD ovalbumin move along the basic membranes of capillaries and arteries after being injected into the corpus striatum in mice.

These findings are clinically significant as beta-amyloid accumulates in the vascular wall of arterioles and arteries, based on observations in patients with cerebral amyloid angiopathy. The accumulation of insoluble amyloid can block this drainage pathway and therefore inhibit the elimination of beta-amyloid and interstitial fluid from the brain in Alzheimer's disease [54]. The size of amyloid deposition is so pronounced that it has been proposed as a natural determinant for peri-arterial drainage pathways [55]. Peri-arterial drainage of liquids and solutes has important effects not only in neurodegenerative diseases but also in immunological CNS diseases [55]. Similar to arteries, veins in the subarachnoid space have pial sheath forming a PVS [42].

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